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Lilia Talarico, M.D. Director
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Document Control Room 6B-30
5600 Fischers Lane
Rockville, MD 20857

IND 25,512: Emitasol® (Metoclopramide) Nasal Spray
Serial Number 107: Request for FDA Review of Clinical Protocol

Dear Dr. Talarico,

We refer to our End-of-Phase II meeting held In this meeting, we discussed the protocol design for our proposed Phase III study, titled " Metoclopramide Nasal Spray for Diabetic Gastroparesis ". The protocol for this study has been revised with respect to the comments made by the Division. We also have incorporated some additional changes that were not discussed at the meeting.

The major revisions to the protocol are summarized as follows:

1. The new title of the study is: "Comparison of the Efficacy and Safety of Emitasol® Nasal Spray Versus Placebo in Patients with Diabetic Gastroparesis"
2. A second metoclopramide intranasal dosing group (10 mg qid) and a placebo nasal spray group have been added to the study. The encapsulated Reglan® Tablet and placebo for Reglan® have been eliminated from the study design.
3. The study will consist of two 4-week treatment phases: Phase A is a randomized, parallel group comparison of two doses of metoclopramide nasal spray (10 mg qid and 20 mg qid), and Phase B is a placebo-controlled withdrawal phase. Patients who complete Phase A will be randomized to one of three groups: Metoclopramide 10 mg qid, metoclopramide 20 mg qid, or placebo nasal spray qid.
4. The primary efficacy endpoint is the change from baseline to the end of the study in the total symptom score during the randomized withdrawal phase. The baseline will be the mean of the last two total symptom scores immediately proceeding the start of the second treatment phase at Days 21 and 29. The end of study measure will be the mean of the last two total symptom scores at Days 50 and 57.
5. To ensure that a total of 156 patients (52 per group) will be randomized into Phase B (52 per group), 200 patients initially will be randomized into Phase A. Fifty-two patients per treatment group will provide 90% power to detect a difference of at least 3.5 points between treatment groups. In the original study design, the planned

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sample size was 250 evaluable patients (125 patients receiving metoclopramide nasal spray 20 mg qid and 125 patients receiving oral Reglan Tablets 10 mg qid).

In addition to the study cited above, we also intend to conduct an 8-week study in diabetic gastroparesis patients in which we will compare the pharmacokinetics of two strengths of Emitasol Nasal Spray and the Reglan® Tablet (10 mg qid). The doses of Emitasol will be the same as those in the study cited above. Both studies will be carried out concurrently.

We hereby submit the latest drafts of the pharmacokinetic and Phase III protocols for your review and comment.

A safety database of approximately 150 patients (104 from the Phase III efficacy study and 45 from the pharmacokinetic study) receiving 8 weeks of intranasal metoclopramide treatment will be provided. Additional safety data from two Phase I studies where 69 patients received at least one 20, 40 or 80 mg single intranasal dose of metoclopramide. and in a Phase III chemotherapy study where approximately 80 patients received multiple single doses (20-80 mg) of metoclopramide over a 16-hour period will be included in the database.

Other single dose and multiple dose acute dosing studies are available, and may be included in the database depending on the availability of source documents/CRFs. This information is unknown at this time.

We would appreciate receiving your comments on an expedited basis.

Please contact me at (732) 676-1270 if you have any questions.

Sincerely,

David Haenick

David Haenick. Ph.D.
Senior Manager
Regulatory Affairs

Enclosure:
•FDA Form 1571
•Protocol No. 25.512-301R titled "Comparison of the Efficacy and Safety of Emitasol® Nasal Spray Versus Placebo in Patients with Diabetic Gastroparesis".
•Protocol No. 25.512-302R titled "Comparison of the Pharmacokinetics and Safety of Emitasol® Nasal Spray versus Orally Administered Reglan® in Patients with Diabetic Gastroparesis".

C: Dr. Laura Lehman (RiboGene. Inc.)